REMARKS

Claim 1 has been amended to be limited to humans and to incorporate the limitations of claim 2. Claim 4 has been amended to be limited to humans and to be independent. Claim 9 has been amended to be limited to humans and to incorporate the limitations of claims 10 and 12. Claims 3, 7, 11, 13, 14, 16-18, 20, and 21 have been amended to correct dependency and/or antecedent basis. Claims 2, 10, 12, 15, 19, 22, and 23 have been canceled without prejudice to or disclaimer of the subject matter contained therein.

No new matter has been entered by these claim amendments.

Rejection Under 35 USC § 112, 1st Paragraph - Enablement

Claims 1-20 and 23-25 are rejected as lacking enablement. Claims 2, 10, 12, 15, 19, and 23 have been canceled, making this rejection moot as applied to these claims. This rejection is respectfully traversed as applied to the pending claims.

The Examiner cites Lucentini (The Scientist 24:20, 2004), Hegele (Arterioscler. Thromb. Vasc. Biol. 22:1058-61, 2002), Corominas et al. (Eur. J. Neuro. 16:413-15, 2009), Kaunisto et al. (Cephalagia 26:1462-72, 2006), Oterino et al. (Neuroreport 17:61-4, 2006), and Joshi et al. (Cephalagia 30:311-20, 2010) for the proposition that the present invention is in the "unpredictable arts" (see, Mycolgen Plant Sci., Inc. v. Monsanto Co. (243 F.3d 1316, 1330 (Fed. Cir. 2001)) and concludes that the claims are broadly drawn, the art is unpredictable, there is a lack of guidance in the specification, and undue experimentation would be required for a person skilled in the art to practice the invention in full scope. Specifically, the Examiner alleges that (1) it is not known whether the studied polymorphisms exist in species other than human. Additionally, the Examiner alleges that (2) the specification provides no association that any alteration in a female sex hormone receptor gene indicates a predisposition for migraine. Finally, the Examiner alleges that (3) it is not clear which polymorphisms or mutations would have the claimed association with migraine.

The claims have now been amended to specifically recite (1) that the method is determined for a human, (2) that the method involves detection of a polymorphism in "exon 8 of a human estrogen receptor (ESR1) gene that encodes codon 594 of an estrogen receptor protein" and/or "at least a fragment of intron 7 of a human progesterone receptor gene," and (3) that the polymorphism are detected "at said codon 594" of exon 8 and/or that "the polymorphism

comprises a 306 base pair insertion in intron 7." As explained in additional detail below, these amendments directly address the concerns raised by the Examiner. Accordingly, in light of the claim amendments and arguments presented below, Applicants respectfully submit that the claimed methods are enabled by the specification.

To satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph, the specification must teach those skilled in the art to make and use the full scope of the claimed invention without undue experimentation. Enzo Biochem, Inc. v. Calgene, Inc., 188 F.3d 1362, 1371, 52 USPQ2d 1129, 1135 (Fed. Cir. 1999); Genentech, Inc. v. Novo Nordisk, A/S, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997); PPG Inds., Inc. v. Guardian Inds. Corp., 75 F.3d 1558, 1564, 37 USPQ2d 1618, 1623 (Fed. Cir. 1996); In re Wright, 999 F.2d 1557, 1561-62, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); In re Vaeck, 947 F.2d 488, 495-96, 20 USPQ2d 1438, 1444-45 (Fed. Cir. 1991). "That some experimentation may be required is not fatal, the issue is whether the amount of experimentation required is 'undue.'" In re Vaeck, 947 F.2d at 495, 20 USPQ2d at 1444. The enablement section of 35 U.S.C. § 112, first paragraph, "requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art." In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). In order to determine whether the present claims are enabled, an analysis of the teachings of the specification must be performed as well as an inquiry into the knowledge of persons of ordinary skill in the art. In re Bowen, 492 F.2d 859, 861, 181 USPQ 48, 50 (CCPA 1974).

The amended claims are generally drawn to methods of determining whether a human individual has a predisposition to migraine, including analyzing a biological sample from the individual for (i) a polymorphism in at least a fragment of exon 8 of an estrogen receptor (ESR1) gene that encodes codon 594 of an estrogen receptor protein and/or (ii) a polymorphism in at least a fragment of intron 7 of a progesterone receptor gene, where the polymorphism comprises a 306 base pair insertion in intron 7. As such, Applicants respectfully submit that the amended claims are enabled by the specification, as described in further detail below.

Detection in Human Individual. As amended, the claims are drawn to a method of "determining whether a human individual has a predisposition to migraine." (emphasis added). Accordingly, the amended claims encompass detection in humans. The studies described in the

specification involve the determination of polymorphisms in human patients (see, pages 17-25). As such, the claimed methods are fully supported by the evidence set forth in the specification.

Specific Polymorphisms. As amended, the claims are drawn to detection of polymorphisms at: (i) a fragment of exon 8 of an estrogen receptor (ESR1) gene that encodes codon 594 of an estrogen receptor protein and/or (ii) a polymorphism in at least a fragment of intron 7 of a progesterone receptor gene, where the polymorphism comprises a 306 base pair insertion in intron 7. Accordingly, the amended claims encompass detection of two specific polymorphisms. Each of the two specific polymorphisms and their association with migraine are set forth in the specification. (see, e.g., page 7, lines 3-9). As such, skilled artisan would have no difficulty in predictably identifying the claimed polymorphisms.

Methods of detecting a polymorphism in a nucleotide sequence according to the amended claims are amply described in the specification, for example, at pages 11-14, and include: nucleic acid sequence amplification (e.g., as described at page 11, line 26 to page 12, line 10) in conjunction with restriction fragment length polymorphism analysis (see, page 12, lines 14-19) and/or direct sequencing (see, page 13, lines 21-25); bidirectional PCR amplification of specific alleles (see, page 12, lines 28-30); allele-specification oligonucleotide hybridization (see, pages 13, lines 1-3); fluorescence-based melt curve analysis (see, page 13, lines 4-15); denaturing gel electrophoresis (see, page 13, lines 16-20); mass spectroscopy (see, page 13, lines 26-29); and microarray analysis (see, page 13, line 30 to page 14, line 15). Accordingly, clear guidance for the detection of a polymorphism is provided.

Additionally, the present description provides working examples of determining whether an individual has a predisposition to migraine, including analyzing a biological sample from the individual for a polymorphism in the estrogen receptor gene and/or the progesterone receptor gene (see, page 17, line 20 to page 24, line 2). As discussed at page 20, lines 21-23, individuals who carry the 594A allele in the ESR1 gene are 1.8 times more likely to suffer from migraine than those who do not carry this allele. Given that an alteration at this codon leads to such a significant alteration in propensity toward migraine, one skilled in the art would readily recognize that other alterations in codon 594 would similarly lead to an increased propensity toward migraine.

Similarly, individuals who carry the progesterone receptor gene insert allele are also 1.8 times more likely to suffer from migraine than those who do not carry this allele (see, page 22,

lines 19-28). In combination, these alleles increase the risk of migraine by a factor of 3, which is greater than the independent effects of these genetic variants on disease susceptibility (see, page 23, line 21 to page 24, line 2). Accordingly, there is no *prima facie* showing that the claimed invention as recited in the amended claims is not enabled.

An enabling disclosure must describe the claimed invention in such a way as to enable the ordinarily skilled artisan to make and use the invention, and this description must be commensurate with the scope of the claimed invention. The test of enablement is not whether experimentation is necessary, but rather if experimentation is necessary, whether it is undue. In re Angstadt, 198 USPQ 214, 219 (CCPA 1976). The test of whether an invention requires undue experimentation is not based on a single factor, but rather a conclusion reached by weighing many factors. In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Factors to be considered in determining whether undue experimentation is required include the quantity of experimentation necessary, the amount of guidance provided in the specification, the presence of working examples of the invention in the application, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability in the art, and the breadth of the claimed invention. Id at 1404. Accordingly, the holding of Wands does not require that an applicant identify every polymorphism in the estrogen receptor gene and/or the progesterone receptor gene that predispose an individual to migraine. Rather, Wands sets out factors to be considered in determining whether undue experimentation is required to practice the claimed method of determining whether a human individual has a predisposition to migraine.

When all of the Wands factors are considered together, it is clear that although some quantity of experimentation may be required to practice the invention as recited in the amended claims, the experimentation would not be undue in view of: (i) the nature of the invention, (ii) the state of the prior art (where detecting a polymorphism in a nucleotide sequence is routine), (iii) the relative skill of those in the art (which is high, as evidenced by the Corominas, Kaunisto, Oterino, and Joshi references cited by the Examiner), (iv) the predictability in the art, (v) the amount of direction provided in the specification (which includes methods of detecting a polymorphism in a nucleotide sequence), (vi) the breadth of the claimed invention (which is limited to a polymorphism in at least a fragment of exon 8 of an estrogen receptor (ESR1) gene that encodes codon 594 of an estrogen receptor protein and/or a polymorphism in at least a fragment of intron 7 of a progesterone receptor gene, where the polymorphism comprises a 306

base pair insertion in intron 7), and (vii) the existence of working examples of determining whether an individual has a predisposition to migraine, including analyzing a biological sample from the individual for a polymorphism in the estrogen receptor gene and/or the progesterone receptor gene. These factors all favor a conclusion that one of skill in the art could practice the claimed invention without undue experimentation.

In view of the above arguments, reconsideration and withdrawal of the rejection under 35 USC § 112, first paragraph is respectfully requested.

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, Applicant is not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. Applicant reserves the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that Applicant has made any disclaimers or disavowals of any subject matter supported by the present application.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

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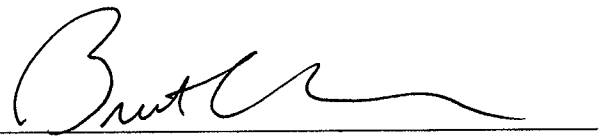
By: 

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